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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/371,347	08/10/99	GRAVEL R	50004/003003

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EXAMINER	
STEADMAN, D	
ART UNIT	**PAPER NUMBER**
1652	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/371,347	GRAVEL ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *9-34* is/are withdrawn from consideration.

5)☒ Claim(s) *3* is/are allowed.

6)☒ Claim(s) *1, 2, and 4-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4,7 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Status of the Application

Claims 1-8 are pending.

Applicant's election without traverse of Group I, Claims 1-8 in Paper No. 10 is acknowledged. Applicants also request that PTO Forms 1449 filed 10/06/2000 and 11/12/2000 in Papers No. 4 and 7, respectively, be initialed and returned. These forms are included in this Office Action.

Claims 9-34 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Drawings

1. The drawings are objected to by the Examiner. Refer to the "Notice of Draftsperson's Patent Drawing Review" (Form PTO 948). Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 4 and 5 (claims 6-8 dependent thereon) are indefinite in the recitation of "high stringency" in claim 4 and "high stringency conditions" in claim 5 as the specification does not clearly define what conditions constitute "high stringency". It is noted that Applicants have described "high stringency" in the specification at page 16, lines 19-23. However, Applicants reference Ausubel et al. for a description of other "high stringency" conditions. As such, it is unclear what Applicant's definition of "high stringency" is. The meaning of this term varies widely in the art depending on the individual situation as well as the person making the determination. Therefore, it is unclear how homologous to the sequence of a gene encoding SEQ ID NO:1 or 41, a sequence must be to be included within the scope of these claims. It is suggested that, for example, Applicants clearly indicate the hybridization conditions considered to "high stringency".

4. Claim 5 (claims 6-8 dependent thereon) recites the limitation "the nucleic acid encoding the methionine synthase reductase". There is insufficient antecedent basis for this limitation in the claim. It is suggested that the term be replaced with, for example, "a nucleic acid encoding a methionine synthase reductase".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a genus of DNA molecules encoding any methionine synthase reductase from mammalian (claim 1) or human sources (claim 2). The specification teaches the structures of only 2 species of polynucleotides encoding methionine synthase reductases, i.e., SEQ ID NO:1 and 41. Moreover, the specification fails to describe any other representative species of methionine synthase reductases by any identifying characteristics or properties other than the functionality of encoding a methionine synthase reductase. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

6. Claims 4-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of DNA molecules that hybridize at high stringency to SEQ ID NO:1 or 41 (claim 4) or that is complementary to at least 50 % of at least 60 nucleotides of SEQ ID NO:1 or 41 that hybridizes at high stringency to SEQ ID NO:1 or 41 (claim 5) and has a mutation or polymorphism and encodes a mutant or polymorphic polypeptide or fragment thereof (claim 6), wherein said mutation is a 4 base deletion from base 1675 of SEQ ID NO:1 (claim 7) or 3 base deletion from base 1726 of SEQ ID NO:1 (claim 8). The genus of cDNAs that comprise the above described cDNA molecules is a large variable genus with the potentiality of encoding many different proteins. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The

specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

7. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding the methionine synthase reductase of SEQ ID NO:1 or 41, a nucleic acid having the sequence of SEQ ID NO:1 or 41 encoding SEQ ID NO:2 or 42, a nucleic acid that hybridizes at high stringency to SEQ ID NO:1 or 41, a nucleic acid having the sequence of SEQ ID NO:1 with bases 1675-1679 deleted, and a nucleic acid having the sequence of SEQ ID NO:1 with bases 1726-1728 deleted, does not reasonably provide enablement for any nucleic acid that encodes any mammalian or human methionine synthase reductase, any degenerate variants of SEQ ID NO:1 or SEQ ID NO:41 encoding SEQ ID NO:2 or SEQ ID NO:42, any nucleic acid that hybridizes at high stringency conditions to a sequence found within the nucleic acid of SEQ ID NO:1 or SEQ ID NO:41, any nucleic acid that is complementary to at least 50 % of at least 60 nucleotides of SEQ ID NO:1 or 41, any nucleic acid that is complementary to at least 50 % of at least 60 nucleotides of SEQ ID NO:1 or 41 containing a mutation or polypeptide, wherein the mutation is a 4 base deletion from base 1675 of SEQ ID NO:1 or a 3 base deletion from base 1726 of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-8 are so broad as to encompass any polynucleotide encoding a mammalian methionine synthase reductase or human methionine synthase reductase, any degenerate variants

of SEQ ID NO:1 or SEQ ID NO:41 encoding SEQ ID NO:2 or SEQ ID NO:42, any nucleic acid that hybridizes at high stringency conditions to a sequence found within the nucleic acid of SEQ ID NO:1 or SEQ ID NO:41, any nucleic acid that is complementary to at least 50 % of at least 60 nucleotides of SEQ ID NO:1 or 41, any nucleic acid that is complementary to at least 50 % of at least 60 nucleotides of SEQ ID NO:1 or 41 containing a mutation or polypeptide, wherein the mutation is a 4 base deletion from base 1675 of SEQ ID NO:1 or a 3 base deletion from base 1726 of SEQ ID NO:1. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. Since the nucleic acid sequence encoding a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and detailed knowledge of the ways in which the polypeptide's structure relates to its function during hybridization. However, in this case the disclosure is limited to a nucleic acid encoding the methionine synthase reductase of SEQ ID NO:1 or 41, a nucleic acid having the sequence of SEQ ID NO:1 or 41 encoding SEQ ID NO:2 or 42, a nucleic acid that hybridizes at high stringency to SEQ ID NO:1 or 41, a nucleic acid having the sequence of SEQ ID NO:1 with bases 1675-1679 deleted, and a nucleic acid having the sequence of SEQ ID NO:1 with bases 1726-1728 deleted. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a polynucleotide's sequence where nucleic acid modifications can be made with a reasonable expectation of success in obtaining the desired

activity/utility are limited in any polynucleotide and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given polynucleotide to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any nucleic acid that hybridizes at high stringency conditions to a sequence found within the nucleic acid of SEQ ID NO:1 or SEQ ID NO:41 because the specification does not establish: (A) regions of the polynucleotide sequence which may be modified without affecting the encoded methionine synthase polypeptide activity; (B) the general tolerance of the polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acids with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any polynucleotide encoding a mammalian methionine synthase reductase or human methionine synthase reductase, any degenerate variants of SEQ ID NO:1 or SEQ ID NO:41 encoding SEQ ID NO:2 or SEQ ID NO:42, any nucleic acid that hybridizes at high stringency conditions to a sequence found within the nucleic acid of SEQ ID NO:1 or SEQ ID NO:41, any nucleic acid that is complementary to at least 50 % of at least 60 nucleotides of SEQ ID NO:1 or 41, any nucleic acid that is complementary to at least 50 % of at least 60 nucleotides of SEQ ID NO:1 or 41 containing a mutation or polypeptide, wherein the mutation is

a 4 base deletion from base 1675 of SEQ ID NO:1 or a 3 base deletion from base 1726 of SEQ ID NO:1. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Leclerc et al. (Proc Natl Acad Sci 95:3059-3064). Claims 4-6 are drawn to a nucleic acid encoding SEQ ID NO:1 or 41 wherein the nucleic acid encodes SEQ ID NO:2 or 42, respectively (claim 3) or a nucleic acid that hybridizes at high stringency to SEQ ID NO:1 or 41 (claim 4). SEQ ID NO:41 and 42 were not present in the specification, drawings, or claims of the parent application (09/232,028) and therefore, do not receive the benefit of the earliest priority date (01/15/99), and instead receive the priority date (08/10/99) of the instant continuation-in-part application (09/371,347). Leclerc teaches an isolated nucleic acid that is 99.9 % identical to SEQ ID NO:41 with a mismatch at nucleotide 66 (A to G) that encodes a protein that is 99.9 % identical to SEQ

ID NO:42 with a conservative substitution (I to M) at amino acid 22. This anticipates claims 4-6 as written.

9. . Claims 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillier et al. (Genome Res 6:807-828, 1996). Claims 4-6 are drawn to polynucleotides that hybridize to SEQ ID NO:1 or 41. Hillier et al. teach a nucleotide that hybridizes to base pairs 1735-2097 of SEQ ID NO:1 and 41 with potential mismatches at nucleotides 2067 and 2082 of SEQ ID NO:1 and 41. This anticipates claims 4-6 as written.

10. Claims 4-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Strausberg (GenBank Accession No. AA279276, direct submission). Claims 4-6 are drawn to polynucleotides that hybridize to SEQ ID NO:1 or 41. Strausberg teaches a nucleotide that hybridizes to base pairs 1054-1407 of SEQ ID NO:1 and 41 with no mismatches, insertions or deletions. This anticipates claims 4-6 as written.

15. Claims 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gulati et al. (J Biol Chem 272:19171-19175, 1997). Claim 1 is drawn to a nucleic acid encoding a mammalian methionine synthase reductase.

Gulati et al. teach "fractionation of crude [porcine] homogenates indicates that at least two redox proteins are required for NADPH-dependent activation of porcine methionine synthase" (p 19171, right column, bottom). Gulati et al. provide a method for partial purification these redox proteins from procine liver homomgenates and a method of assaying fractions for the activation of methionine synthase due to reduction by these redox proteins (p 19172, left column under *Enzyme Preparations* and *Methionine Synthase Assays*). Gulati et al. also teach "the redox

activators are separate from methionine synthase, contrary to the suggestion that the activation system may be integral to it" (p 19173, right column, paragraph 2). Gulati et al. further teach that mutations in the auxillary protein that activates methionine synthase represents an additional locus for genetic defects that can lead to hyperhomocysteinemia and that their study "provides the first description of the physiological activation system employed by mammalian methionine synthase. The identities of the individual components await the purification and characterization of these proteins" (p 19175, left column, bottom).

The skill of an ordinary artisan in the field of molecular biology at the time of the invention was such that the artisan could use conventional techniques to: 1) using chromatographic techniques or gel electrophoresis, separate contaminating proteins from a target protein; 2) obtain a partial amino acid sequence of a purified polypeptide; 3) synthesize a degenerate polynucleotide probe based on the partial amino acid sequence; 4) use the polynucleotide probe to screen a cDNA or genomic library and identify a full length cDNA or genomic clone; 5) construct expression vectors comprising the isolated cDNA or genomic clone; and 6) transform a host cell with an expression vector comprising the isolated cDNA or genomic clone. One of ordinary skill in the art at the time the invention was made would have been motivated to isolate a polynucleotide encoding a wild-type and mutant mammalian methionine synthase reductase because of the teaching of Gulati et al. who taught that genetic mutations in the protein that activates methionine synthase represents an additional locus for genetic defects that can lead to hyperhomocysteinemia.

11. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

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